--43. **(New Claim)** A kit of claim 6, wherein said first primer is the ~~nucleic acid~~ of SEQ. ID. No: 5.

A4 44. **(New Claim)** A kit of claim 43, ~~further~~ comprising an appropriate amount of *HinfI* restriction enzyme.--

REMARKS:

Applicants note that claims 1-14 and 40-42 are considered free of the prior art.

The IL-1B (+6912) mutation is in fact a G to C change. As filed, the specification inadvertently described the +6912 mutation as a C to G change. This is an accidental reversal of the actual mutation. A C to G change at position +6912 is not possible because there is already a "G" at that position in the wild-type IL-1B sequence (Figure 1, SEQ. ID. No:1). Applicants respectfully request correction of this inadvertent error as set forth in the amendments to the specification given above. In addition, Figure 2 as filed does not indicate the G to C change at +6912. Applicants request that a replacement Figure 2, provided herewith and showing the appropriate change, be accepted to replace Figure 2 as filed.

Claims 5, 9, 10, and 34-36 are amended. Claim 35 has been amended to recite "cytosine" instead of "guanine" "at a position equivalent, relative to the surrounding sequence, to position 6912". Support for a cytosine at position +6912 can be found, for example, on page 6, line 32. See also the amendments to the specification presented above. The amendments of claims 5, 9, 10, 34 and 36 are merely clarifying and grammatical corrections. Claim 9 has been amended to list different SEQ ID Nos. for the claimed primers, because the numbers given in the claim as filed are all off by one and do not correspond to the appropriate nucleotide sequence. Support for new claim 43 can be found, for example, in claim 9 as originally filed and on page 3 of the specification. Support for new claim 44 can be found, for example, in claim 10 as originally filed and on page 3 of the specification. Accordingly, no new matter has been introduced. In

amending or canceling claims, Applicants reserve the right to pursue all claims as originally filed in future applications.

RESTRICTION REQUIREMENT:

Applicants affirm the election with traverse of group I, claims 1-14 and 34-36, made on 10/4/99 during a telephonic conference. Applicants also concur with the Examiner in including claims 37-42 among the elected claims.

CLAIMS 37-42 REJECTED UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ENABLEMENT

The Examiner argues, "(Claims) 37-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

Claims 37-39:

The Examiner continues:

> "With respect to claims 37-39, the invention encompasses transgenic non-human animals of any species. The transgene may be expressed in any quantity, but the animal is not characterized by any phenotype which distinguishes it from any other animal...The specification fails to teach or provide examples of how to use a transgenic animal which is not characterized by any phenotype that readily distinguishes it from a wild type version of the animal."

Applicants traverse this rejection. Applicants respectfully remind the Examiner that "as long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement for Section 112 is satisfied. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24

(CCPA 1970)." *Training Materials for Examining Patent Applications with respect to 35 U.S.C. Section 112, First Paragraph-Enablement, Chemical/Biotechnical Applications.* Applicants submit that the specification meets these criteria for enablement.

The specification describes many possible uses for the claimed transgenic animals. For example, page 27 of the specification teaches uses including: identifying IL-1β agonists or antagonists, confirming the safety and efficacy of a candidate therapeutic, determining the effects of higher endogenous levels of IL-1β, etc. One of skill in the art would appreciate that, to serve as a system for screening for IL-1β agonists or antagonists a transgenic animal need only have a measurable phenotype that is dependent upon carrying the IL-1B gene. If a potential pharmaceutical modulates the phenotype, the agent can be considered either an agonist or an antagonist.

Applicants assert that a transgenic animal expressing the claimed IL-1B allele would have a measurable phenotype. IL-1β is a powerful and well-conserved regulator of many physiological processes. Applicants note that many mice expressing wild-type human IL-1B are not viable because of the overwhelming effects of IL-1β (Lai et al., p. 290, first paragraph, cited by the Examiner). Lai et al. also present a series of phenotypes resulting from the expression of human IL-1B in mice. Additionally, the specification provides (as noted by the Examiner) many methods for creating transgenic animals that express IL-1B (+6912) allele 2 at different levels or in different patterns.

Applicants conclude that the specification does teach at least one method for making and using the claimed invention, and that the methods provided are sufficiently varied and comprehensive as to provide enablement that is commensurate with the scope of the claims. Accordingly, reconsideration and withdrawal of this rejection of claims 37-39 is requested.

Applicants note that Lai et al. is mentioned solely to establish the likelihood of obtaining a phenotype and not as part of a discussion of prior art.

Claims 40-42:

The Examiner suggests:

> With respect to claims 40-42, the invention encompasses a transgenic animal comprising SEQ ID NO:2...Claims 40-42 encompass transgenic animals which have a phenotype characteristic of an inflammatory disorder...The instant specification, while providing extensive information concerning how one might control certain aspects of transgene expression, does not teach what level of transgene expression is required to produce the claimed phenotype, or how to reproducibly achieve that level in any or all transgenic animals.

The Examiner further suggests that generating transgenic animals with particular gene expression levels is a highly uncertain art.

Applicants respectfully disagree with the Examiner's statements. Lai et al. (cited by the Examiner) demonstrate that mice expressing human IL-1B have many inflammation-related phenotypes. Therefore, it is likely that the transgenic animals of claims 40-42 would also have inflammation-related phenotypes, including phenotypes that mimic those of human diseases.

Nonetheless, to expedite prosecution, Applicants have canceled claims 40 and 41.

With respect to claim 42, Applicants contend that, as argued above, the specification does provide methods which would allow one of skill in the art to make transgenic animals with a phenotype characteristic of an inflammatory disease generally. Lai et al. show that transgenic mice expressing human IL-1B show various defects and alterations of their immune systems and inflammatory responses. For this reason, and reasons presented above, Applicants maintain that claim 42 is enabled.

Applicants request reconsideration and withdrawal of this rejection.

CLAIMS 40-42 REJECTED UNDER 35 U.S.C. §112, FIRST PARAGRAPH, WRITTEN DESCRIPTION:

The Examiner argues, "Claims 40-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

The Examiner further contends:

> It is not reasonable to expect that the complete structure of a transgenic animal could be described, therefore the inquiry required by this portion of the written description guidelines is interpreted to be whether the phenotypic consequences of altering the genotype have been described. In this case, the specification describes phenotypic consequences, but does not provide a disclosure which enables a skilled artisan to produce any of the animals of the claimed genus.

Applicants traverse this rejection. Claims 40 and 41 are canceled (see above), and accordingly, the discussion is limited to claim 42. The revised Interim Guidelines for Examination of Patent Applications under 35 U.S.C. §112, paragraph 1, Federal Register, Vol. 64, No. 244, states that the written description requirement for a genus claim may be satisfied by providing sufficient written description for a representative number of species by: (1) actual reduction to practice; **or** (2) reduction to drawings, or disclosure of relevant identifying characteristics; sufficient to show that the applicant was in possession of the claimed genus.

The specification and original claims disclose many relevant identifying characteristics for the transgenic animals of claim 42. The claims note that the transgenic animal must be "non-human", "contains and expresses an isolated nucleic acid" of SEQ. ID. No:2. The state of the art is such that there is absolutely no uncertainty about any of these distinguishing characteristics. One of skill in the art can determine with complete confidence whether an animal possesses "an

isolate nucleic acid". Therefore, many concrete and unambiguous identifying characteristics have been provided. Accordingly, Applicants maintain that claim 42 satisfies the written description requirements.

The Examiner has argued that a skilled artisan could not make a transgenic animal of claim 42, and therefore that the art is very uncertain. Applicants respectfully submit that whether or not one could make the claimed animal is not a question of written description but is instead a question of enablement as dealt with above.

For these reasons Applicants request reconsideration and withdrawal of this rejection under 35 U.S.C. §112, paragraph one, written description.

CLAIMS 1-14 REJECTED UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ENABLEMENT.

The Examiner argues, "Claims 1-14...are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

With respect to claims 1-14, the Examiner argues that support for linkage between IL-1B allele 2 (+6912) and specific inflammatory diseases comes only by reference to other publications. The Examiner notes:

> In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application. MPEP 608.01(p). See *In re Fouche*, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971).

Applicants respectfully traverse this rejection. Applicants maintain that the material incorporated by reference is not essential. Applicants note that the criteria for "essential material" are as follows: "Essential material" is defined as that which is necessary to (1) describe

the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode." MPEP §608.01(p)(1)(A).

Applicants assert that the specification explicitly provides the essential material with respect the association between IL-1B allele 2 (+6912) and specific inflammatory diseases. First, the specification presents data establishing that IL-1B allele 2 (+6912) is linked to alleles of the IL-1 (33221461) haplotype (see Example 6, pages 44-46). Second, the specification describes diseases that are associated with the IL-1 (33221461) haplotype (see page 46). Because IL-1B allele 2 (+6912) is linked to alleles of the IL-1 (33221461) haplotype, and alleles of the IL-1 (33221461) haplotype are linked to various diseases and conditions, it follows mathematically that IL-1B allele 2 (+6912) is associated with the same diseases and conditions. Lastly, methods for identifying IL-1B allele 2 (+6912) are presented in example 2. This disclosure therefore describes the associated diseases (description of the invention, as per criterion #1, above), establishes that these diseases are associated with IL-1B allele 2 (+6912) and provides methods for identifying the IL-1B allele 2 (+6912) (enablement, as per criterion #2, above).

The information referred to by the Examiner as being incorporated by reference is merely previously published data demonstrating that alleles of an IL-1 haplotype are associated with various diseases and conditions. This data is properly considered background information. A skilled artisan wishing to practice or understand the invention need not know how the association between the IL-1 haplotype and a disease or condition was first established. It is sufficient to know that this fact has been established. Therefore, Applicants maintain that all essential information is provided explicitly in the specification and that no essential information is incorporated by reference to a non-patent publication.

The Examiner further contends, "In light of the art-recognized lack of biochemical evidence linking overexpression of IL-1β to any disease, and the failure of the instant specification to provide such evidence, a skilled artisan would be required to perform undue experimentation in order to use the invention as claimed."

Applicants respectfully disagree. Applicants remind the Examiner that the requirement for enablement under 35 U.S.C. §112, first paragraph, is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further, the

scope of enablement must only bear a "reasonable correlation" to the scope of the claims. *In re Fischer*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Applicants maintain that the teachings of the specification and the knowledge of one skilled in the art are sufficient to allow a skilled artisan to practice the claimed invention without undue experimentation.

The teachings of the specification provide a powerful combination of biochemical and genetic evidence to support the claims. The application presents data that the IL-1B (+6912) allele 2 causes overproduction of IL-1β. The application further demonstrates that IL-1B (+6912) allele 2 is associated with many diseases. The combination of linkage to diseases and a mechanistic effect on IL-1β strongly suggests that this particular allele is a causative mutation for these diseases. Applicants respectfully suggest that additional biochemical experimentation is quite unlikely to provide clearer evidence of linkage between overexpression of IL-1B and a disease state. Biochemical evidence is necessarily obtained in an in vitro setting and is therefore subject to many artifacts that can arise in vitro.

For these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §112, first paragraph.

CLAIMS 34-42 REJECTED UNDER 35 U.S.C. §112, SECOND PARAGRAPH.

The Examiner contends, "Claims 34-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

The Examiner further suggests,

> Claims 34-42 are indefinite because the scope of claim 34 is unclear. Claim 34 is drawn to "an isolated nucleic acid as shown in SEQ ID NO:2." This can be interpreted two ways. The nucleic acid of claim 34 either consists of SEQ ID NO:2, or it comprises nucleotides sequences encompassed by SEQ ID NO:2. The second interpretation encompasses sequences as long as SEQ ID NO:2 and as short as a dinucleotide. If the first interpretation is employed, then claims 35 and 36 are indefinite because they are drawn simultaneously to the complete sequence of SEQ ID NO:2 and to fragments of that sequence.

Applicants respectfully traverse this rejection. Applicants suggest that neither of the two above interpretations of claim 34 applies to the claim as amended. Claim 34 is amended to

recite: "An isolated nucleic acid comprising the nucleotide sequence as shown in SEQ ID. No. 2." This language clearly indicates that the claim is not intended to encompass fragments of SEQ ID. No.2. Claims 35 and 36 have been amended to be independent of claim 34 and these claims are intended to encompass fragments of SEQ ID. No.2.

The Examiner notes, "Claim 35 is indefinite because it is drawn to polynucleotides of less than 6912 nucleotides in length which must contain a guanine at position 6912."

Applicants note claim 35 has been amended to more clearly define what is meant by "position 6912".

In view of these amendments, Applicants respectfully request withdrawal and reconsideration of these rejections under 35 U.S.C. §112, second paragraph.

CLAIMS 34-39 REJECTED UNDER 35 U.S.C. §102(b) AND §103(a)

The Examiner has rejected claims 34-39 as unpatentable over various references including Clark, et al. (GenBank Accession No. X04500), Clark, et al. (Nuc. Acids Res. 14(20):7897-7914, 1986), and Lai, et al. (Cytokine 8(4):288-293, 4/1996). Each of these references relates to the wild-type sequence of IL-1B which has a G at position +6912 or transgenic animals expressing such a sequence.

Applicants note that the claims as amended now relate to a nucleic acid sequence with a C at the position equivalent to +6912. Therefore, these references no longer anticipate or in any way teach or suggest the invention as claimed in claims 34-39. For these reasons, Applicants request reconsideration and withdrawal of these rejections under 35 U.S.C. §102(b) and §103(a).

CONCLUSION

For the reasons presented, Applicants respectfully request that the pending rejections be reconsidered and withdrawn. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited.

If there are any fees in connection with the filing of this Response, please charge the fees to our **Deposit Account No. 06-1448.** If a fee is required for an extension of time under 37 C.F.R. §1.136, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
Foley, Hoag & Eliot LLP

Dated: June 29, 2000

Beth E. Arnold
Reg. No. 35,430
Attorney for Applicants

Patent Group
Foley, Hoag & Eliot LLP
One Post Office Square
Boston, MA 02109-2170
Tel.: (617) 832-1000
Fax: (617) 832-7000